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FINAL
PROGRESS REPORT
(Unclassified Section)

for

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701

from

The Johns Hopkins University
Applied Physics Laboratory
Johns Hopkins Road
Laurel, Maryland 20723

on

A STUDY OF LOW LEVEL LASER RETINAL DAMAGE

1 March 1990

B. F. Hochheimer

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FOREWORD

In conducting the research described in this report, the investigator(s) adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences-National Research Council.



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INTRODUCTION

The objectives of this program were to document retinal changes due to low level laser irradiation. Methods to accomplish this that could potentially be used on human subjects were investigated.

This program started 1 January 1978 and continued until 31 December 1989, an 11 year period. From January 1985 until December 1989, a 5 year period, this program's objectives were changed and the results were classified. This report covers the first 6 years of the program. The classified work is covered in a separate document.

During this time the Army Medical Research and Development Command funded 30% of time for the principal investigator and approximately 20% of time for a technical assistant. Mr. S. A. D'Anna was this assistant for all 11 years. Since time of the principal investigator was required for progress reports and yearly proposals for future funding, only about 15 months of actual research over this 6 year period were Army-funded. During this period the remaining time of the principal investigator was funded by internal APL IR&D funds or by the National Institutes of Health (NIH).

I wish to acknowledge at this time the people who helped on various aspects of this program.

JHU Personnel

Mr. Robert Flower and I collaborated on studies of infrared dyes for angiography, photographic retinal reflectance measurements, and light scatter in the eye.

Mr. Henry Kues made polarization retinal photographs of human subjects and purified the various dyes we used.

Mr. Donald Mitchel, a design machinist, made all of our fundus camera modifications.

Dr. Leonard Parver and I had many fruitful discussions on retinal light damage mechanisms.

Dr. Gregory Bulkley provided me with information on oxygen reperfusion injury in the body.

Non-JHU Personnel

Mr. Jack Lund, Col. Edward Beatrice and
Mrs. Rebecca McHenry from LAIR

David Sliney from the Aberdeen Proving Grounds

Dr. Ralph Allen from Brooks Air Force Base

Dr. William Ham from the University of Virginia at
Richmond

Dr. Myron Wolbarsht from Duke University

During this period there were two NIH grants that I worked on that influenced my thinking on the Army's problems. Dr. Joseph Calkins and I studied stress-testing of the cornea by holography. This study led to several published papers on retinal light damage by ophthalmic instruments. Mr. Jerome Lutty and I investigated the efficiency of the combination of hematoporphyrin

and light to kill malignant tumors of the eye. This work helped in my understanding of the destructive role of oxygen on human tissue.

The work that is reported here was documented in yearly progress reports and in a series of papers published by the principal investigator. These papers are listed in the reference section of this report. The contents of the yearly progress reports are also indicated in case they are desired for reference.

The earliest work on this program relied heavily on previous work that had been done over a number of years. An Argon Ion laser photocoagulator was made for Dr. Arnal Patz (JHMI) before they became commercially available. A fundus camera was designed and built to do fluorescein cineangiography.^{1,2} This camera used rather low level retinal illumination and was not just a modified commercial camera. I had an NIH contract to find useful dyes for retinal angiography.⁷ This led to the use of several dyes which enabled a better view of the choroidal circulation than does fluorescein.^{3,4,14} Retinal polarized light photography was shown to be useful for early detection of macular diseases under an NIH grant.^{8,22} Retinal reflectivity was measured over very small areas using photographic techniques.⁶ We thus already had a wide range of tools and experience to apply to the Army's problems before this program started.

During the period in which this program was funded I developed methods to measure a wide variety of fluorescein fluorescence parameters. This was done under APL-IR&D funding. An understanding of the data available from these measurements would undoubtedly have led to a better understanding, at a molecular level, of the degree of retinal integrity. I had hoped to apply these techniques to the detection of low level laser

retinal damage in the retina. The work on fluorescein fluorescence parameters measurements was stopped when I found that, contrary to popular opinion, fluorescein is a potent phototoxic agent in the retina.²⁶ The damage threshold for blue light retinal damage is lowered by a factor of ten after an intravenous injection of fluorescein dye, for at least one tested situation.

In this report the test procedures will be outlined and the results of these tests will be given. The actual data is contained in both the referenced published papers and in the yearly progress reports. It seemed redundant to submit reams of already-submitted data.

The program results will be described in sections arranged according to the techniques used and not in strict chronological order. This was done to make the results easier to follow.

The order that will be followed is given below. A separate section will be devoted to each of the following topics.

- A. Equipment Modifications
- B. Photographic Documentation of Retinal Damage
- C. Measurement of Reflectance Changes in the Retina
- D. Retinal Light Damage Mechanisms
- E. Dyed Artificial Tear Films for Eye Protection
- F. Light Scatter in the Eye

G. Other Projects Related to the Problem of Retinal Light
Damage

1. Corneal Holography
2. Hematoporphyrin Studies
3. Fluorescein Fluorescence Measurements

EQUIPMENT MODIFICATIONS^{P2, P6, P8}

When the program started in 1978 we had a standard Zeiss fundus camera that had been slightly modified. Fixed polarizers could be placed in both the input and return light paths for retinal polarization photography. Narrow bandpass filters could be placed in the illumination light path for retinal photography at any wavelength from 400 to 1000 nm. Angiography could be done using a wide range of dyes that fluoresced at wavelengths from 500 to 830 nm. For dyes with suitably wavelength-separated fluorescence bands retinal angiograms could be taken with two dyes simultaneously.⁵ A Nikon fundus camera, fitted with a 70 mm camera for moderately high resolution fundus photography, was also available.¹⁵ In order to induce laser retinal burns a commercial Coherent Radiation Inc. photocoagulator was used.

In 1979 a narrow field of view 70 mm camera was adapted to the Zeiss camera to obtain high resolution fundus photographs. Light from the retina could also be analyzed with a monochromator-photomultiplier system on the Zeiss camera. The Zeiss camera could also be used with a pulsed, Q-switched, YAG laser to precisely place laser burns on the retina. A stereotaxic animal holder for use with our camera was also designed and constructed in 1979.

The original Zeiss camera had illumination optics with excessive spherical and chromatic aberration. In 1980 these optics were replaced with a well-corrected optical system so that very small retinal areas could be illuminated for retinal reflectance measurements. That year a CW-YAG laser and a Gallium Arsenide laser were also adapted for retinal irradiation through the Zeiss camera. A movie camera was also adapted to be used in place of the 70 mm camera when desired.

In 1981 a Hewlett-Packard 9845 computer was purchased and all of the operational functions of the Zeiss camera and the data acquisition were put under computer control.

A fiber optics light source was added in 1982 so that extremely small retinal areas could be illuminated. A monochromator filtered light source was also added to do fluorescence measurements. The monochromator, in the output path, that we used in 1979 had low throughput and was replaced with a rotating interference monochromator which had high throughput but only moderate resolution. A 50 mW HeNe laser was adapted to the camera, mostly for hematoporphyrin studies. It was also used for laser safety studies.

In 1983 an Argon Ion laser was purchased and incorporated into the camera. This laser could be operated in either a CW mode or modulated at frequencies up to 50 MHz for fluorescence decay measurements.

A second Zeiss camera became available in 1985 and was used with a Xenon arc light source mainly for the hematoporphyrin studies. It also provided a source for retinal irradiation at any bandwidth limited wavelength from 400 to 1000 nm.

In 1986 classified work was started and continued up to the present time.

PHOTOGRAPHIC DOCUMENTATION OF RETINAL DAMAGE^{P1, P2, P3}

Almost all of our earliest retinal light damage documentation was done with photographic film. This was all that was available to us in 1978. We tried the techniques we were familiar with.

Angiograms were taken with several different fluorescent dyes. The fluorescence of these dyes was in the yellow, red and near-infrared. As the retina is viewed with shorter wavelengths the outer portions (nearest the cornea) become more and more transparent. With red and infrared angiograms the choroidal circulation is easily seen even with a heavily pigmented retina. None of the dyes proved to be any better than fluorescein for laser damage detection. Fluorescein is a very small molecule, much smaller than the other dyes we used, and it leaks easily from damaged blood vessels. Fluorescein leakage at the site of retinal burns is readily visible.

When the retina is photographed through crossed polarizers a fan-shaped figure is seen over the macular area. We have shown that the visibility of this figure is a good indicator of macular health. The use of this technique to detect small laser lesions, even near the center of the macula, is not useful. It is only when rather large retinal areas are damaged that the technique is useful.

Retinal photographs taken with various discrete wavelengths of light have often been used to separate the visibility of the different layers of the retina. We used this technique with narrow bandpass interference filters to examine retinas damaged with an argon ion laser. While there were differences to

be seen, depending on wavelength, no wavelength seemed to be an improvement over fluorescein angiography for retinal damage detection.

Lund & Beatrice ("Spectral Photography of Retinal Lesions," Supp. Invert. Ophth. & Vis. Sci., April 1979, p 51) used narrow bandwidth photography to investigate the time history of retinal damage by a gallium arsenide laser. This laser emits in the near-infrared and presumably is damaging to the choroid.

In 1980 we used cinephotography to view the retina while it was being damaged by a pulsed YAG laser. For pulse energies that were close to the damage threshold, immediate retinal changes could be seen that disappeared within one hour's time. These changes often were not seen until after 30 seconds of irradiation during a 60 second irradiation period.

During this "photographic" period a method was developed to record high resolution iris angiograms using a simple adapter for a Zeiss camera.²³ We still get calls asking for these adapters; four are being manufactured today in our shops for people all around the country.

We also showed that the visibility of the nerve fiber layer over the retina could be enhanced with polarized light and with an absorbing intravenous dye (Patent Blue).

Retinal photographs taken with a standard fundus camera are limited in resolution by the eye, the camera optics and light source, and by the recording medium, which is usually film. During our work on retinal photography it became apparent that the film was the limiting resolution factor. The eye and the camera optics contribute to a loss in resolution but are not usually the

limiting factor. We exhaustively studied the characteristics of film to find the film with the highest product of sensitivity times resolution.¹⁷ Since the amount of light going into the eye is limited by either safety considerations or camera limitations the best results are obtained when all of the light returning from the eye is used to expose a film with a high sensitivity-resolution product. The size of the retinal image must be such that there is enough light to expose the film optimally. This usually occurs when the retinal image in a fundus camera is greatly enlarged. Thirty-five millimeter Tri-X film is ordinarily used only because of convenience and because Tri-X film has a wide exposure latitude.

We found that retinal resolution could be decreased from 15 microns to less than 5 microns with optimum conditions. We then showed that small retinal lesions were more easily visualized with improved resolution.

MEASUREMENT OF REFLECTANCE CHANGES IN THE RETINA^{P4, P5, P6, P7, P8}

Changes due to laser damage can be seen in retinal photographs because of a local change in retinal reflectivity. This reflectivity change may be over a small spectral range or over the whole visible and near-infrared regions where the optics of the eye are transparent.

We had used photographic techniques with bandpass filtering to measure retinal reflectivity over small areas of a monkey retina and attempted to do this with laser damaged retinas. Photography has limited dynamic range and poor repeatability; it is unsuitable to measure small changes; however, small areas can be repeatedly measured with high spatial accuracy.

Short and long term reflectivity changes were measured photographically in minimally laser damaged retinas. With time, the reflectivity of the damaged area approaches that of neighboring undamaged areas and differences cannot be detected even though its position is well known. In addition, the precision of the measurements proved to be unacceptably low.

Photoelectric detectors, compared with film, have high sensitivity, wide dynamic range, and high precision. With a monochromator and photomultiplier attachment to our fundus camera, we attempted a long-term study of retinal reflectivity changes. When the reflectivity of a damaged area approaches that of neighboring undamaged area it cannot be seen and the ability to position the retinal correctly relative to the photomultiplier is lost.

We did show that photoelectric recordings of changes in retinal reflectivity could be made during the time the burn was being produced but this was not very useful information.

In 1985 and 1986 the retinal reflectivity of a large number of wild and domestic animals was measured using our well-developed photoelectric recording methods. This survey of a wide variety of retinal types has proved informative for the Army.

RETINAL LIGHT DAMAGE MECHANISMS^{P3,P4,P5}

The Army Medical Research and Development Command would like to establish realistic laser safety standard guidelines for use by military personnel. In order to do this it is absolutely necessary that the mechanisms of damage be known and understood. As an example of mistakes that can be made, consider the early laser safety standards that did not account for the long-term irradiation blue light retinal damage found by Ham and by Sperling.

It is possible that second harmonic light can be generated in the eye by laser irradiation and second harmonic light be a damaging component. We looked for second harmonic light generated in the retina by irradiation with a pulsed 1.06 micron YAG laser. No second harmonic was detectable by our instruments. We next looked for second harmonic generation in the cornea. With irradiation by the pulsed YAG laser we could detect second harmonic light at 532 nm.²¹ The conversion efficiency is so small that it does not seem possible that this could be a cause for concern.

A likely candidate mechanism for retinal damage by light is the generation of singlet oxygen, an excited state of an oxygen molecule. Singlet oxygen is a potent poison for any body tissue. Singlet oxygen can be generated from the reaction of light with many different types of molecules in the presence of oxygen. Melanin is one such molecule and the retina is an oxygen-rich, melanin-rich, tissue.

Singlet oxygen may decay by fluorescence or by a reaction with another molecule. If the decay is by fluorescence,

photons are emitted and, if in sufficient numbers, may be detected. If the decay is by reaction with another molecule, that molecule is often severely damaged.

Some singlet oxygen fluorescence photons are emitted in the near-infrared and some even in the red portion of the visible spectrum. We irradiated a monkey retina with light and looked for fluorescence at the visible fluorescence wavelengths. Nothing could be detected. This does not mean that there is no singlet oxygen, only that fluorescence, if there, was not detectable with our equipment.

It is assumed that the reaction of light with hematoporphyrin results in the production of singlet oxygen.²⁷ We looked at the retinal damage resulting from light input to the eye at 630 nm after an animal was injected with hematoporphyrin. There were some similarities and some differences from a retina damaged by blue light. Again an inconclusive result.

There is still another process whereby the retina could be damaged by singlet oxygen. When light hits the retina it is known that there is a significant amount of oxygen used in the photoreceptor detection process. Some tissues, the brain for example, can be damaged by depriving it of blood circulation which lowers the brain oxygen content. In the normal brain are a large number of singlet oxygen scavengers. When the oxygen content drops, the scavengers also disappear. If the brain is reperfused with oxygenated blood, singlet oxygen is generated spontaneously. Since there is a lack of singlet oxygen scavengers the singlet oxygen attracts brain cells and kills them. This could be happening in the eye.

DYED ARTIFICIAL TEAR FILMS FOR EYE PROTECTION^{P3, P5, P6}

We were asked by the Army in 1980 to investigate the possibility of using artificial tears with absorbing dyes for protection from laser radiation. Several dyes have high absorption coefficients at 532 nm, the second harmonic of YAG lasers. These include Phloxine B, Erythrosine B and Eosin Y. These are readily soluble in Hypotears and could offer an order of magnitude protection.

These dyes may be phototoxic although there appears to be no short term toxicity. A factor of ten improvement in safety seems to be a lot but it really is not; several orders of magnitude are needed. In addition, the protection is only short-term, a few tens of minutes at most before the tears are washed from the eye. Any dye will also be only good over a single wavelength range.

LIGHT SCATTER IN THE EYE^{P4,P5,P6,P7}

Knowledge of the amount of light scattered in the eye is important not only for a basic understanding of the visual process, but also for an understanding of a variety of other problems. It is impossible to compute retinal reflectivity without knowing the amount of scattered light in the eye. Retinal reflectivity is always measured, for a live animal eye, by comparison with an artificial eye of known retinal reflectivity. If the light scatter is high, the computed retinal reflectivity is always too low.

In order to model a laser damage mechanism it is necessary to know how much light actually strikes the retina where you think it does. To do this not only must the amount of scattered light be known, but also the angular distribution of the scattered light must be known.

If a laser beam hits the retina at some distance away from the macula, there may still be macular effects due to stray light in the eye. This is very important in flash blindness conditions and in laser photocoagulation procedures.

Before this program with the Army began I had measured the spectral reflectivity of monkey eyes. I assumed there was negligible scattered light. When we attempted to track the appearance of laser burns on the retina for a long time after the burns were made, it became apparent that scattered light in the eye was hindering our measurements.

In 1981 a formula was derived which predicted the internal scattered light in the eye. This model considered only the

light internally reflected as if the eye were an integrating sphere.¹⁰ This model indicated that internal light scattering in the eye was negligible.

In 1983-84 the scattered light in the eye was measured by illuminating a very small retinal area and measuring the amount of light reflected from areas at a distance from the illuminated area. Our data indicated that the light scattered in the eye by the cornea, aqueous, lens and vitreous was the 70-80% range. Our data was not corrected for the double passage of light through the eye. This correction would reduce the measured scattered light to 50 to 60% of the incident light.

This very large amount of scattered light in the eye was confirmed in our 1986-1989 classified work for the Army which was only indirectly concerned with scattered light.

RELATED PROJECTS^{P3,P5}

A. Corneal Wound Healing, Stress Testing

Dr. Joseph Calkins and I implemented a holographic method to monitor corneal wound stress to be used after corneal transplants to determine the optimum time to remove sutures.^{11,20} We compared the amount of light hitting the retina from our instrument to that from operation microscopes, slit lamps, flash lamps and overhead surgical lamps. We found that our instrument was quite safe but that the ophthalmic instruments were not. Retinal lesions were easily made in a monkey eye with either an operation microscope or a slit lamp and these lesions were visible a year later.^{9,12,13,16,18,19,24,25}

B. Hematoporphyrin Phototherapy for Malignant Tumors

In this project Mr. Jerome Lutty and I investigated methods to improve the use of photodynamic therapy for treatment of eye tumors. This study led to considerations of oxygen toxicity in the retina induced by light alone or by the interaction of light with phototoxic dyes.

C. Fluorescein Fluorescence Measurements

For almost the entire period of this project I pursued methods of using fluorescence measurements to indicate the degree of retinal integrity. Fluorescence polarization, excitation and fluorescence spectra, fluorescence decay time and fluorescence intensity changes can all be measured in the retina following an intravenous injection of sodium fluorescein. This data can be used to infer the ratio of free to bound fluorescein, local pH,

local pO_2 , fluorescein concentration, membrane transport phenomena, dye triplet state concentration and oxygen excitation. These methods looked extremely promising as diagnostic tools for retinal diseases until I found that fluorescein dye can be phototoxic in the retina. Fluorescein can decrease the amount of blue light needed to produce retinal lesions by over a factor of ten in the cornea, iris and retina.

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